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FASTTRACK CLINICAL RESEARCH
Atrial fibrillation

Nurse-led vs. usual-care for atrial fibrillation

E.P.J. Petra Wijtvliet [1,2], Robert G. Tieleman[2], Isabelle C. van Gelder [3], Nikki A.H.A. Pluymaekers [1], Michiel Rienstra [3], Richard J. Folkeringa [4], Patrick Bronzwaer[5], Arif Elvan [6], Jan Elders[7], Raymond Tukkie [8], Justin G.L.M. Luermans [1], A.D.I. Thea Van Asselt[9], Sander M.J. Van Kuijk [10], Jan G. Tijssen[11], and Harry J.G.M. Crijns [1]*; for the RACE 4 Investigators†

[1]Department of Cardiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Centre, P. Debyelaan 25, 6229 HX Maastricht, The Netherlands; [2]Department of Cardiology, Martini Hospital, Van Swietenplein 1, 9728 NT Groningen, The Netherlands; [3]Department of Cardiology, University of Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands; [4]Department of Cardiology, Medical Centre Leeuwarden, Henri Dunantweg 2, 8934 AD Leeuwarden, The Netherlands; [5]Department of Cardiology, Zaans Medical Centre, Kon. Julianaplein 58, 1502 DV Zaandam, The Netherlands; [6]Department of Cardiology, Isala Hospital, Dokter van Heesweg 2, 8025 AB Zwolle, The Netherlands; [7]Department of Cardiology, Canisius Wilhelmina Hospital, Weg door Jonkerbos 100, 6532 SZ Nijmegen, The Netherlands; [8]Department of Cardiology, Spaarne Hospital, Haarlem, The Netherlands; [9]Department of Epidemiology, University of Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands; [10]Department of Clinical Epidemiology, Medical Technology Assessment, Maastricht University Medical Centre, P. Debyelaan 25, 6229 HX Maastricht, The Netherlands; and [11]Amsterdam University Medical Centre, Location AMC, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

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Background Nurse-led integrated care is expected to improve outcome of patients with atrial fibrillation compared with usual-care provided by a medical specialist.

Methods and results We randomized 1375 patients with atrial fibrillation (64 ± 10 years, 44% women, 57% had CHA_2DS_2-VASc ≥ 2) to receive nurse-led care or usual-care. Nurse-led care was provided by specialized nurses using a decision-support tool, in consultation with the cardiologist. The primary endpoint was a composite of cardiovascular death and cardiovascular hospital admissions. Of 671 nurse-led care patients, 543 (81%) received anticoagulation in full accordance with the guidelines against 559 of 683 (82%) usual-care patients. The cumulative adherence to guidelines-based recommendations was 61% under nurse-led care and 26% under usual-care. Over 37 months of follow-up, the primary endpoint occurred in 164 of 671 patients (9.7% per year) under nurse-led care and in 192 of 683 patients (11.6% per year) under usual-care [hazard ratio (HR) 0.85, 95% confidence interval (CI) 0.69 to 1.04, $P = 0.12$]. There were 124 vs. 161 hospitalizations for arrhythmia events (7.0% and 9.4% per year), and 14 vs. 22 for heart failure (0.7% and 1.1% per year), respectively. Results were not consistent in a pre-specified subgroup analysis by centre experience, with a HR of 0.52 (95% CI 0.37–to 0.71) in four experienced centres and of 1.24 (95% CI 0.94–1.63) in four less experienced centres (P for interaction <0.001).

Conclusion Our trial failed to show that nurse-led care was superior to usual-care. The data suggest that nurse-led care by an experienced team could be clinically beneficial (ClinicalTrials.gov NCT01740037).

Trial Registration number ClinicalTrials.gov (NCT01740037).

Keywords Atrial fibrillation • Cardiovascular mortality and morbidity • Nurse-led care • Stroke • Heart failure • Usual-care • Randomized clinical trial

* Corresponding author. Tel: +31 43 3875093, Fax: +31 43 3877081, Email: hjgm.crijns@mumc.nl

† A complete list of Investigators in the RACE 4 trial is provided in the Supplementary material online.

Introduction

Patients with atrial fibrillation are usually seen by a cardiologist. To improve cardiovascular outcomes in these patients, guidelines advocate multidisciplinary management, patient empowerment and shared decision-making.[1–3]. Also, clinical care for atrial fibrillation provided by a mono-disciplinary specialist may become unaffordable. One manner to implement improvements in patient care is through the co-ordination by a nurse specialized in atrial fibrillation. Nurse-led care is expected to be less resource-intensive and potentially reduces events over and above usual-care. However, it is uncertain whether in clinical practice nurse-led care is effective since data are limited and studies do not provide conclusive evidence.[4–9] Therefore, we conducted a multicentre, randomized trial, RACE 4 (Rate Control vs. Electrical Cardioversion Trial 4—Nurse-led Care vs. Usual-care), to find out whether in patients newly referred for management of atrial fibrillation, nurse-led care would be superior to usual-care provided by a cardiologist in reducing cardiovascular mortality and cardiovascular hospitalization.

Methods

We conducted this superiority trial in the cardiology departments of eight hospitals in the Netherlands, including two academic hospitals, five non-academic teaching hospitals and one non-teaching hospital. Among these, four hospitals had previous experience with nurse-led care. The trial was initiated by the investigators and co-ordinated by the Maastricht University Medical Centre. The trial was approved by the institutional review board at the medical centre; the review board at each of the participating sites approved the protocol (Supplementary material online). All the patients provided written informed consent. An independent data and safety monitoring board reviewed independently and in a blinded fashion the accumulating safety and efficacy data at regular intervals during the trial. The trial was supported by Netherlands healthcare insurance companies (DSW, ACHMEA, and CZ), Boehringer Ingelheim, Bayer, Pfizer, Bristol-Myers Squibb, and Daiichi-Sankyo, but all had no role in the design or execution of the trial; company representatives did not review the protocol or the manuscript. The writing committee wrote the manuscript, and all the steering committee members made the decision to submit it for publication. The authors had unrestricted access to the data and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol.

Study participants

From December 2012 through November 2017, we enrolled adults (≥18 years of age) with first-detected atrial fibrillation referred to the outpatient cardiology clinic by their primary care physician or a non-cardiology specialist for cardiological management. All patients were in a stable condition and qualified as being candidates for either nurse-led care or usual-care. Patients were excluded if they had an episode of unstable heart failure or acute coronary syndrome within 3 months before inclusion. Patients who recently underwent cardiac surgery or in whom cardiac surgery was planned were excluded. Further details regarding the inclusion and exclusion criteria are provided in Supplementary material online, *Table S1*.

Randomization and treatment

After providing written informed consent, all patients were randomly assigned in a 1:1 ratio stratified by centre to nurse-led care or usual-care provided by a cardiologist. Randomization was performed with the use of a centralized Web-based system. After randomization, the first visit was planned with the specialized nurse or the cardiologist per randomized group. Nurse-led care included treatment of patients by a specialized nurse using guidelines-based decision-support software (CardioConsult AF®, Curit Software, Groningen, The Netherlands) ensuring comprehensive treatment of atrial fibrillation and associated conditions, covering cardiovascular risk factor management, antithrombotic treatment, rate control, and rhythm control[4,10,11] (Supplementary material online, *Figure S1*). Complete cardiological diagnostic tests and treatments were installed during the first outpatient visit. All test results were extensively discussed, and treatments adapted as needed and confirmed onsite with the supervising cardiologist, all during the first visit. To enhance patients' adherence the nurse provided psychosocial support as well as personalized education on pathophysiology, symptoms, and complications of atrial fibrillation. Usual-care consisted of routine outpatient management by a cardiologist without a specified clinical pathway. An overview of nurse-led care and usual-care is provided in Supplementary material online, *Figure S2*.

Follow-up

Follow-up visits under nurse-led care were achieved at 3, 6, and 12 months, and yearly thereafter. Blood pressure and the electrocardiogram were recorded, and psychosocial support and educational intervention were repeated during follow-up visits. Medication was adjusted as needed. Upon the nurse's request, the cardiologist provided supervision during follow-up visits. Changes in anticoagulation therapy, or in rate and rhythm control were done in consultation with the cardiologist. At patients' request, additional visits either by telephone or in-person were performed at the outpatient department. Patients in the usual-care arm were followed yearly or were referred back to their primary care physician, all at the discretion of the attending cardiologist. Follow-up was terminated within a maximum period of 5 years and 10 months or until 1 October 2018, whichever came first.

Endpoints

The primary endpoint was a composite of cardiovascular death and hospital admission for arrhythmias, heart failure, thromboembolic events, major bleeding, acute coronary syndrome, or life-threatening effects of drugs. Definitions of the components of the primary Endpoint are reported in Supplementary material online, *Table S2*. Secondary endpoints included the level of implementation of care according to the guidelines assessed after the first visit, patients' knowledge on atrial fibrillation using the Netherlands Knowledge Scale on Atrial Fibrillation, [12] quality of life using the University of Toronto Atrial Fibrillation Severity Scale (AFSS)[13], the Patient Activation Measure self-management score[14], and cost-effectiveness. All primary endpoint events were adjudicated by an independent clinical endpoint committee (not aware of the randomized treatment assignments) that used the above-mentioned definitions of the components of the primary endpoint. A complete overview of all secondary endpoints of the trial is listed in the Supplementary material online, *Table S3*.

Statistical analysis

The primary hypothesis of the trial was that nurse-led care would be superior to usual-care with respect to the primary endpoint. The sample size determination was event-driven. The design assumptions included a 2 years event rate of 11.2% for nurse-led care and 16.0% for usual-care. We calculated that 246 composite primary endpoints would provide the trial with 80% power to statistically detect the expected treatment benefits at a two-sided significance level of 0.05. Monitoring of the occurrence

of the primary endpoints over time indicated that 1375 patients with a minimum follow-up of 1 year, would provide at least 246 endpoints.

Analyses were performed according to the intention-to-treat principle. Patients without any electrocardiographic documentation of atrial fibrillation before the first visit were excluded from the analysis, as were patients with full withdrawal of informed consent.

Event rates over time were displayed using the Kaplan–Meier method. Hazard ratios (HR) with 95% confidence intervals (CI) and *P*-values were calculated using the Cox proportional hazards model. Follow-up of the patients was censored at the study termination as defined above or at the last day of known clinical status. All reported secondary and subgroup analyses were pre-specified. Categorical variables were tested using Fisher's exact test, and between-group differences for proportions and 95% CIs were calculated with the Wald Z method. Continuous variables were tested with the independent two sample *t*-test.

Results

Patients

Of the 1375 patients who had undergone randomization, 686 were assigned to nurse-led care and 689 to usual-care, and 671 and 683 were included in the primary analysis, respectively (Supplementary material online, *Figure S3*). Overall the characteristics of the patients at inclusion were well-balanced between the two groups (*Table 1*). The mean (±SD) age was 64 ± 10 years, 891 patients (66%) were male, 766 (57%) had an increased risk of stroke as reflected by a CHA_2DS_2-VASc score of two or higher and 106 patients (8%) had risk of bleeding as suggested by a HAS-BLED score of three or higher. For extended baseline characteristics see Supplementary material online, *Table S4*.

Endpoints

Over a median follow-up of 37 months, the primary endpoint occurred in 164 of 671 patients (9.7% per year) under nurse-led care and in 192 of 683 patients (11.6% per year) under usual-care (HR 0.85, 95% CI 0.70–to 1.05, $P = 0.12$; *Take home figure*, panel A). There were seven vs. three patients with cardiovascular death (0.4% and 0.1% per year), 124 vs. 161 with hospitalizations for arrhythmic events (7.0% and 9.4% per year), and 14 vs. 22 patients with heart failure hospitalization (0.7% and 1.1% per year), in the nurse-led vs. usual-care group, respectively (*Table 2*). Non-cardiovascular mortality amounted 14 (2%) and 14 (2%) patients, and cardiovascular emergency department visits occurred in 86 (13%) and 72 patients (11%), all respectively.

The adherence to seven guidelines-based recommendations on diagnostic procedures and treatments, counting each recommendation separately, was 61% under nurse-led care and 26% under usual-care. For virtually all patients at least two recommendations were implemented whilst nurse-led care performed significantly better than usual-care with regards to implementation of three or more recommendations (Fig. *1A*). There was no difference between nurse-led care and usual-care concerning implementation of oral anticoagulation or rhythm control therapy (Fig. *1B*). However, the implementation of diagnostic procedures (echocardiography, blood pressure measurements, thyroid and renal function testing and assessment of glucose level) was much better under nurse-led care than under usual-care. Therefore, the low cumulative adherence under usual-care (Fig. *1A*) relates particularly to lack of cardiovascular risk assessment including measuring blood pressures, renal function and glucose intolerance (Fig. *1B*).

The scores on the knowledge scale were not significantly different at 1 year of follow-up between nurse-led care and usual-care (7.3 ± 1.6 and 7.4 ± 1.5, difference -0.08, 95% CI, -0.2 to 0.3), as were AFSS quality of life scores (4.8 ± 5.2 and 5.1 ± 5.4, difference 0.35, 95% CI, -0.36 to 1.07), and scores on patient self-management (61.6 ± 17.1 and 61.8 ± 15.7, difference 0.2, 95% CI -2.0 to 2.4), all respectively. At 2 years of follow-up, nurse-led treatment was marginally more costly without a significant difference in QALYs (Supplementary material online, *Figure S4*).

Between-group differences in the occurrence of the primary endpoint under nurse-led care and usual-care in various pre-specified subgroups are shown in *Figure 2* and *Take home figure*, panel B. There was heterogeneity for centre experience which showed a HR favouring nurse-led care in experienced centres (HR 0.52, 95% CI 0.37–to 0.71), and a HR disfavouring nurse-led care in less-experienced centres (HR 1.24, 95% CI 0.94–1.63), with a *P*-value for interaction of <0.001. Other treatment effects were consistent among the other predefined subgroups. Data illustrating differences in centre experience are provided in Supplementary material online, *Figures S5, S6* and *Tables S5, S6*.

Treatment

There was no difference between treatment groups concerning implementation of anticoagulation. In total, 543 (81%) nurse-led care and 559 (82%) of usual-care patients were appropriately treated with oral anticoagulation. On the other hand, 30 (4.5%) nurse-led and 31 (4.5%) usual-care patients were treated with oral anticoagulants without a calculated stroke risk (i.e. over-treatment) whereas in 98 (14.6%) and 93 (13.6%) patients anticoagulants were inappropriately withheld (i.e. under-treatment), respectively.

The use of rate control medication did not differ between groups (Supplementary material online, *Table S7*). The mean heart rate at 3 months, i.e. after installing rate control therapy was 88 ± 17.7 and 88 ± 18.9 beats per minute (mean difference 0.4, 95% CI -4.4 to5.1) under nurse-led and usual-care, respectively. Rhythm control was applied more often in the nurse-led care group compared with usual-care. The number of consultations per treatment group is shown in Supplementary material online, *Table S8*.

Discussion

We found that among patients recently referred for management of first-detected atrial fibrillation, nurse-led care did not significantly reduce the risk of cardiovascular death or hospital admission compared with usual-care. Remarkably, there was a lack of effect of nurse-led care on patient knowledge and quality of life. Nevertheless, exploratory analyses suggested that in experienced centres, nurse-led care was better than usual-care. Given the comparable event rates during the entire follow-up between the two approaches, nurse-led care is a safe manner of providing care for patients with atrial fibrillation.

Guidelines-based recommendations for the examination of the aetiology of atrial fibrillation, associated cardiovascular conditions, stroke prevention, and rhythm control therapy were well-

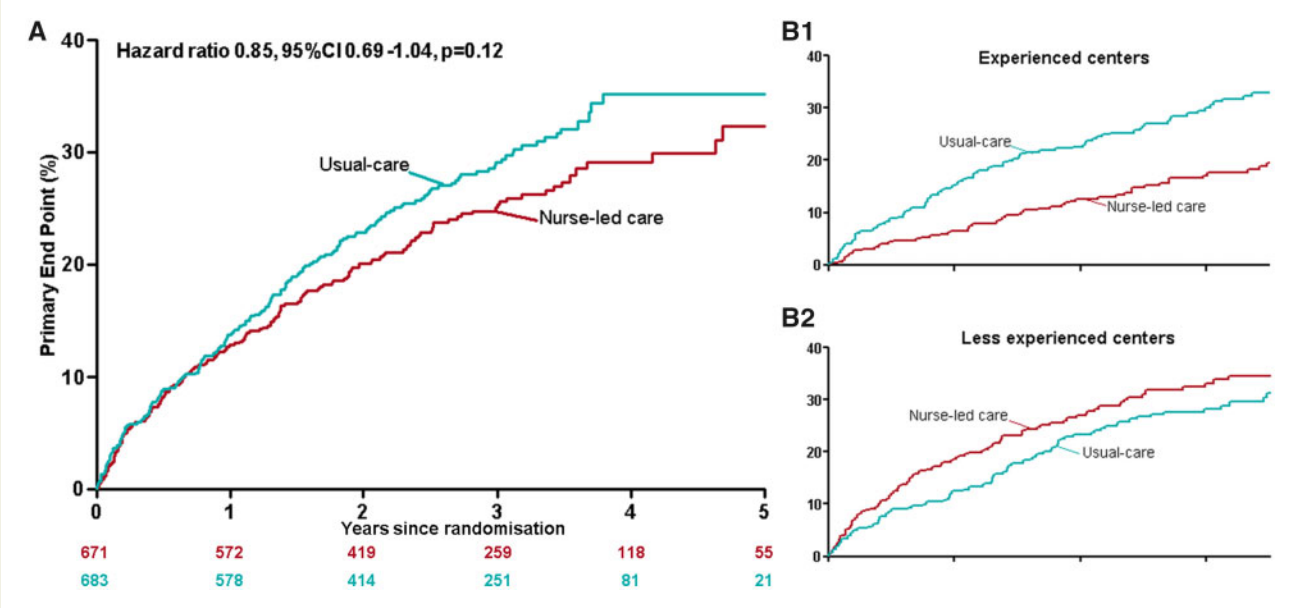
Table 1 Characteristics of the patients at baseline, according to the assigned treatment

Characteristic	Nurse-led care ($n = 671$)	Usual-care ($n = 683$)
Age (years)	64 ± 10	64 ± 11
Male sex, no. (%)	450 (67)	441 (65)
Duration of AF (days)[a]	14 (7–22)	13 (7–21)
Paroxysmal/non-paroxysmal AF, no. (%)	410 (61)/166 (25)	429 (63)/140 (20)
Symptoms at first visit outpatient clinic, no. (%)	324 (48)	319 (47)
Hypertension, no. (%)	329 (49)	316 (46)
History of heart failure, no. (%)	93 (14)	66 (10)
Diabetes, no. (%)	72 (11)	59 (9)
Ischaemic stroke or transient ischaemic attack, no. (%)	56 (8)	42 (6)
Haemorrhagic stroke, no. (%)	2 (0)	2 (0)
Coronary artery disease, no. (%)	40 (6)	37 (5)
Valvular heart disease, no. (%)	22 (3)	36 (5)
Peripheral artery disease, no. (%)	19 (3)	8 (1)
Hyperthyroidism, no. (%)	14 (2)	6 (1)
Chronic obstructive pulmonary disease, no. (%)	63 (9)	62 (9)
Malignancy, no. (%)	53 (8)	73 (11)
CHA_2DS_2-VASc score,[b] no. (%)		
0	162 (24)	173 (25)
1	122 (18)	131 (19)
≥2	387 (58)	379 (56)
HASBLED-score, no. (%)		
≥3	49 (7)	57 (8)
Body mass index, kg/m^2	28 ± 5	28 ± 5
Systolic blood pressure, mmHg	139 ± 20	143 ± 19
Diastolic blood pressure, mmHg	83 ± 11	84 ± 1
Echocardiographic left atrial size, long axis, mm	40 ± 6	40 ± 6
Left ventricular ejection fraction, %	55 ± 9	55 ± 9

Plus-minus values are means ± SD. Congestive heart failure, hypertension, an age of 65–74 years, diabetes, and vascular disease are each assigned one point, and previous stroke or transient ischaemic attack and an age >75 years are assigned two points. The HAS-BLED score is a measure of bleeding risk in patients with AF on anticoagulants, with a score ranging from 0 to 9 and higher scores indicating greater risk. Hypertension, abnormal renal function, abnormal liver function, previous stroke, previous bleeding, labile international normalized ratio (INR), age over 65 years, prior alcohol, or drug usage and use of antiplatelet drugs or non-steroidal anti-inflammatory drugs are each assigned one point. Echocardiographic data were available in 94% of patients in nurse-led care and 81% in usual-care. Numbers do not always add up to 100% for characteristics not listed or missing variables at baseline.
[a]Median, 25–75% range.
[b]The CHA_2DS_2-VASc score is a measure of the risk of stroke in patients with AF, with scores ranging from 0 to 9 and higher scores indicating a greater risk.
AF, atrial fibrillation; TIA, transient ischaemic attack.

implemented under nurse-led care and less well under usual-care (Fig. 1). Despite this difference, we did not find a statistically significant impact on the primary endpoint. Note that the implementation difference was specifically found for recommendations which may lack direct impact on our primary outcome. In contrast, recommendations directly preventing severe events, including stroke or ventricular proarrhythmia, were fulfilled equally. The profile of our patients in terms of cardiovascular risk was mild with CHA_2DS_2-VASc score <2 in 43% of patients, and the overall event rate was accordingly low. Under those circumstances a lack of implementation may not immediately affect outcome. Conversely, when patients exhibit more co-morbidities, correct implementation of diagnostic and treatment procedures as warranted by nurse-led care, may become crucial.[5,6,15–17]

The primary endpoint was driven by admission for arrhythmias, notably atrial fibrillation, which occurred much less under nurse-led care. Reasons for a lower hospitalization rate for arrhythmia recurrence may include better reassurance of patients by the nurse,[18] more patients on rhythm control therapies, or better rate control in addition to optimal implementation of diagnostic procedures and treatment of co-morbidities.[19,20] In nurse-led care, nurses spent more time on informing patients (Supplementary material online, *Table S8*), including providing reassurance about the inconvenience and presumed risks of recurrences of atrial fibrillation. Focus on ameliorating atrial fibrillation symptoms is important and in that respect reducing heart rate during a recurrence or in patients with chronic atrial fibrillation is important.[21] A better rate control did, however, not play a role, since use of rate control medication did not differ and heart rates while in atrial fibrillation were similar in both approaches. In contrast, under nurse-led care, there was a higher use of rhythm control therapies. The relatively low-risk profile of patients gave



Take home figure (*A*) Primary endpoint of the trial. (*B*) The incidence of the primary endpoint over time in experienced (*B1*) and less-experienced centres (*B2*).

Table 2 Primary endpoint

Endpoint	Nurse-led care (*n* = 671)	Usual-care (*n* = 683)
Composite endpoint, no. (%)	164 (24) (9.7% per year)	192 (28) (11.6% per year)
Cardiovascular death	7 (1.0) (0.4% per year)	3 (0.4) (0.1% per year)
Cardiac arrhythmic, no. (%)	1 (0.1)	1 (0.1)
Vascular non-cardiac, no. (%)	6 (0.9)	2 (0.3)
Cardiovascular hospitalizations		
Arrhythmic events, no. (%)	124 (18.5) (7.0% per year)	161 (23.6)(9.4% per year)
Atrial fibrillation	115 (17.1)	138 (20.2)
Atrial flutter	4 (0.6)	12 (1.8)
Supraventricular arrhythmia	0 (0.0)	4 (0.6)
Syncope	11 (1.6)	14 (2.0)
Sustained ventricular tachycardia	1 (0.1)	2 (0.3)
Heart failure, no. (%)	14 (2.1) (0.7% per year)	22 (3.2) (1.1% per year)
Acute coronary syndrome, no. (%)	7 (1.0) (0.4% per year)	11 (1.6) (0.6% per year)
Ischemic TEC, no. (%)	15 (2.2) (0.8% per year)	12 (1.8) (0.6% per year)
Stroke/TIA	16 (2.4)	13 (1.9)
Systemic embolism	0 (0.0)	1 (0.1)
Major bleeding, no. (%)	13 (1.9) (0.7% per year)	10 (1.5) (0.5% per year)
Life-threatening effects of drugs, no. (%)	5 (0.7) (0.3% per year)	3 (0.4) (0.1% per year)

The tabulation of the composite primary endpoint includes the first event for each patient, whereas the tabulations of component end points include all such events. More extensive information on endpoints in subgroups is presented in the Supplementary material online, *Table S4*.
TEC, thromboembolic complications; TIA, transient ischaemic attack.

ample opportunity to implement rhythm control safely. There was no significant issue with appropriate application of guidelines-based rules for providing rhythm control in both groups, but rhythm control therapy was implemented more frequently by the nurse aiming to ameliorate arrhythmia symptoms. An effective understanding of the goals (and explanation of the risks and what to expect from rhythm control therapy) may have reduced the need for hospital admissions, especially when the patient understands that a recurrence does not equal treatment failure or need for immediate intervention.[18]

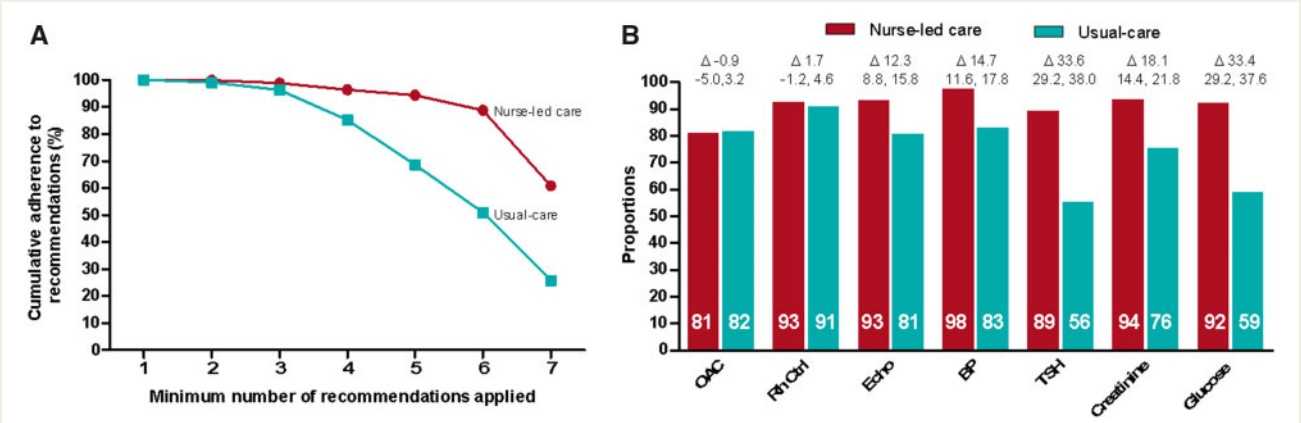


Figure 1 (*A*) Cumulative adherence counting the percentage of patients in whom at least 1–7 guidelines recommendations were applied. (*B*) Adherence to specific recommendations from the guidelines. For definitions of appropriateness of application of guidelines recommendations see Supplementary material online, *Figure S2*). The Wald Z method was used to calculate rate differences and 95% confidence intervals. BP, blood pressure; Echo, echocardiogram; OAC, oral anticoagulation; Rh Ctrl, rhythm control; TSH, thyroid stimulating hormone.

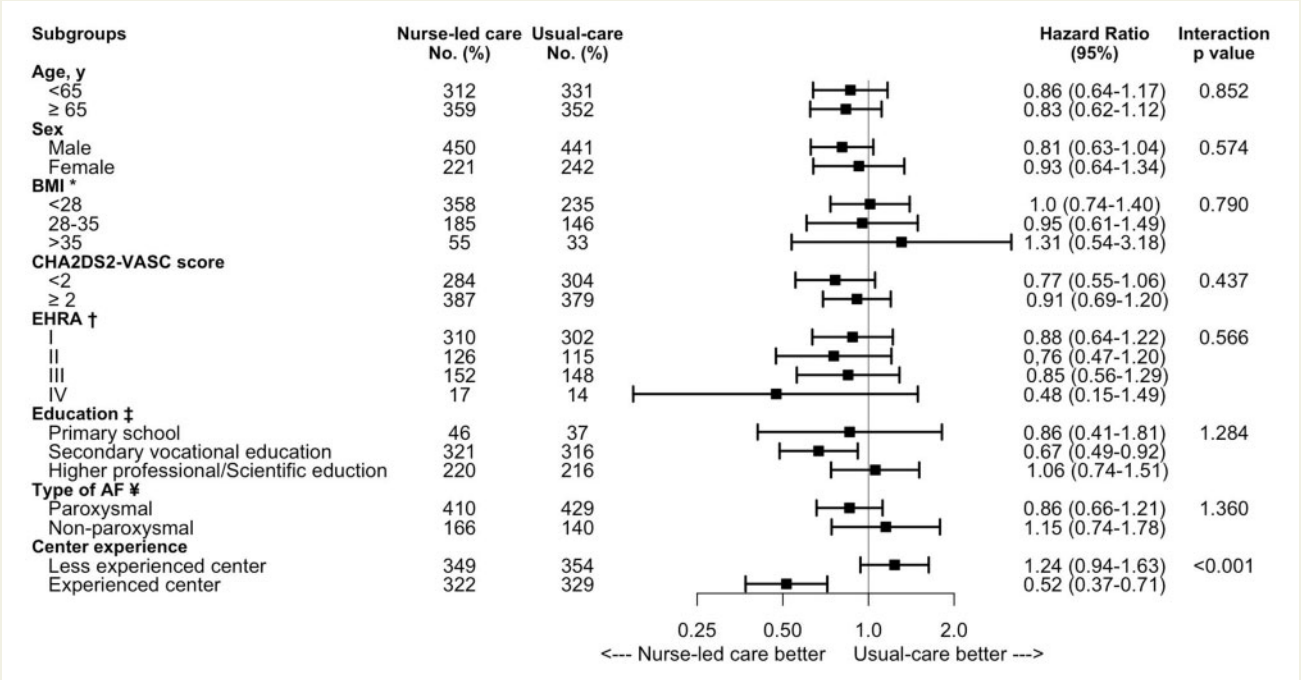


Figure 2 Subgroup analyses of the primary endpoint. AF, atrial fibrillation; BMI, body mass index; EHRA, European Heart Rhythm Association score.

Being anchored to the nurse, patients may have improved their health behaviour just because they know that the nurse closely follows their performance and checks their knowledge of atrial fibrillation (Hawthorne effect).[22] This effect is, in fact, desirable and should be considered an integral part of nurse-led care. On the other hand, in view of the lack of an effect of education on knowledge of atrial fibrillation, such Hawthorne effect may—unfortunately—not have been large in the present study. If anything, the effects of nurse-led care may have been diluted because the cardiologists in our study provided better usual-care because they were aware of their participation in the trial (annulling Hawthorne effect in the control group). Nevertheless, generally at most only half of attending cardiologists are experienced and, therefore, education has become a key both for cardiologists and allied professionals[23].

Nurse-led care was implemented significantly better than usual-care but it was not perfect, especially not on anticoagulation. Almost

15% of patients were under-treated and up till 5% of patients were over-treated. This is remarkable especially since nurses received an electronic advice on antithrombotic treatment. Patients' preference[24] certainly may have played a role, but equally important is the shared decision-making process between nurse and doctor, which may have led to defective antithrombotic management on the advice of the cardiologist.[8] This interpretation is supported by the fact that the extent of over- and under-treatment was the same in both arms of the study.

Heterogeneity between centres was considerable concerning experience in nurse-led care since four centres were proficient including the presence of experienced nurses and well-interacting supervising doctors having at least 1 year of team experience in nurse-led care, and four centres with less experience. The variation seen with implementation of nurse-led care in our study reflects the absence of a consensus description of what integrated care for atrial fibrillation should include.[25,26] It also supports the notion that training is key to obtain excellent results and especially a focus on team-based integrated care approaches seems important[2,8,27].

Limitations

The difference in site experience led to heterogeneity in the treatment benefit which may impede the interpretation of the trial. The influence of the cardiologist on the nurse and the various Hawthorne effects may have diluted the benefit of nurse-led care. Unfortunately, we did not document the reasons for deviating from the electronic management advice.

Conclusion

Our trial failed to show that nurse-led care was superior to usual-care in patients with atrial fibrillation. The results of the subgroup analysis suggest that nurse-led care by an experienced team could be clinically beneficial.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: E.P.J.W., I.C.V.G., R.J.F., P.B., A.E., J.E., R.T., A.D.I.A., S.M.J.K., and J.G.P.T. declare no competing interests. R.G.T. reports grants and personal fees from Boehringer Ingelheim, Bristol-Meyers Squibb, Pfizer, and Daiichi-Sankyo and grants from Bayer during the conduct of the study. N.A.H.A.P. reports grants from Boehringer Ingelheim, Medtronic, Bayer, Pfizer, Bristol-Myers Squibb, Daiichi-Sankyo, and grants from Netherlands Health Insurance companies DSW, ACHMEA, and CZ, during the conduct of the study, all to the institution. M.R. reports grants from Netherlands Cardiovascular Research Initiative funded by Dutch Heart Foundation, outside the submitted work. J.G.L.M.L. reports grants from the Netherlands Cardiovascular Research Initiative funded by the Dutch Heart Foundation, grants from Boehringer Ingelheim, Medtronic, Abbott, Bayer, Pfizer, Bristol-Myers Squibb, Daiichi-Sankyo, and Biotronik, and grants from the Netherlands Health Insurance companies DSW, Achmea, and VGZ, all to the institution, and personal fees from Medtronic, outside the submitted work. H.J.G.M.C. reports grants from the Netherlands Cardiovascular Research Initiative: an initiative with support of the Dutch Heart Foundation, CVON 2014-9: Reappraisal of atrial fibrillation: interaction between hyperCoagulability, electrical remodelling, and vascular destabilization in the progression of atrial fibrillation (RACE V) outside the submitted work; and grants from Boehringer Ingelheim, Medtronic, Abbott, Bayer, Pfizer, Bristol-Myers Squibb, and Daiichi-Sankyo, and from the Netherlands Health Insurance companies DSW, Achmea, and VGZ, during conduct of the study, and all to the institution.

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